



PTO/SB/08A (10-01)

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Substitute for form 1449A/PTO

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

(use as many sheets as necessary)

Sheet

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of

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**Compleat if Kn wn**

Applicati n Number	10/612,171
Filing Date	7/1/2003
First Named Inv ntor	Tosaya, Carol A.
Art Unit	
Examiner Name	
Attorney Docket Number	02017A

**U.S. PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code <sup>2</sup> (if known)			
	2	US-5,478,857	12/26/1995	Clemens et al.	Prior Art
	3	US-5,750,349	05/12/1998	Suzuki et al.	Prior Art
	4	US-5,837,853	11/17/1998	Takashima et al.	Prior Art
	5	US-5,886,051	03/34/1999	Bergeron, Jr. et al.	Prior Art
	6	US-5,889,042	03/03/1999	McLean et al.	Prior Art
	7	US-5,955,317	09/21/1999	Suzuki et al.	Prior Art
	8	US-5,962,463	10/05/1999	Nitsch et al.	Prior Art
	9	US-6,028,066	02/22/2000	Unger	Prior Art
	10	US-6,043,224	03/28/2000	Lee et al.	Prior Art
	11	US-6,080,582	06/27/2000	Alkon et al.	Prior Art
	12	US-6,190,691	02/20/2001	Mak	Prior Art
	13	US-6,300,085	10/09/2001	Alkon	Prior Art
	15	US-5,908,480	11/09/1999	Rubenstein et al.	Prior Art
	16	US-6,264,625	07/24/2001	Rubenstein et al	Prior Art
	17	US-6,383,159	05/07/2002	Saul et al	Prior Art
	20	US-6,001,331	12/14/1999	Caprathe et al.	Prior Art
	21	US-3,942,531	03/09/1976	Hoff et al.	Prior Art
	22	US-4,311,147	01/19/1982	Hausler et al.	Prior Art
	23	US-4,486,680	12/02/1984	Bonnet et al.	Prior Art
	24	US-4,526,168	07/02/1985	Hassler et al.	Prior Art

**FOREIGN PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
		Country Code <sup>3</sup> - Number <sup>4</sup> - Kind Code <sup>5</sup> (if known)				
/	1	WO 95/19178 PCT	07/20/1995	Research Foundation for Mental Hygiene	Prior Art	
/	18	WO 97/26919 PCT	07/31/1997	Warner-Lambert Co.	Prior Art	
/	19	WO 97/41856	11/13/1997	MA Institute of Technology	Prior Art	
/	46	WO 94/23308 PCT	10/13/1994	General Electric	Prior Art	
/	48	WO 98/07373	02/26/1998	Brigham & Women's Hospital	Prior Art	
/	55	WO 02/09608 A2	02/07/2002	Brigham & Women's Hospital	Prior Art	
/	56	EP 1 175 920 A1	01/30/2001	Board of Regents, University of Texas	Prior Art	

Examiner  
SignatureDate  
Considered

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<sup>1</sup>Applicant's unique citation designation number (optional). <sup>2</sup>See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04.

<sup>3</sup>Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup>For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup>Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup>Applicant is to place a check mark here if English language Translation is attached.

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<b>Substitute for form 1449B/PTO</b>  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> <i>(use as many sheets as necessary)</i>				<b>Complete if Known</b>	
				<b>Application Number</b>	10/612,171
				<b>Filing Date</b>	7/1/2003
				<b>First Named Inventor</b>	Tosaya, Carol A.
				<b>Group Art Unit</b>	
				<b>Examiner Name</b>	
<b>Sheet</b>	<b>2</b>	<b>of</b>	<b>4</b>	<b>Attorney Docket Number</b>	02017A

<b>OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS</b>			
<b>Examiner Initials*</b>	<b>Cite, No.</b>	<b>Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.</b>	<b>T<sup>2</sup></b>
/	14	DeMattos, Ronald B., et al., "Brain to Plasma Amyloid- $\beta$ Efflux: A Measure of Brain Amyloid Burden in a Mouse Model of Alzheimer's Disease", <u>Science</u> , Vol. 295, 22 March 2002, pp. 2264-2267.	
/	32	Miller, Douglas L. and Jawaid Quddus, "Lysis and Sonoporation of Epidermoid and Phagocytic Monolayer Cells by Diagnostic Ultrasound Activation of Contrast Agent Gas Bodies", <u>Ultrasound in Medicine and Biology</u> , Vol. 27, No. 8, 2001, pp. 1107-1113.	
/	47	Malcolm, A.L. and G.R. ter Haar, "Ablation of Tissue Volumes Using High Intensity Focused Ultrasound", <u>Ultrasound in Medicine and Biology</u> , Vol. 22, No. 5, 1996, pp. 659-669.	
	51	Clement, G. and K. Hynynen, "Micro-Receiver Guided Transcranial Beam Steering", <u>IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control</u> , Vol. 49, No. 4, IEEE Institute of Electrical and Electronics, pp. 447-453.	
/	52	Behrens, S., et al, "Transcranial Ultrasound-Improved Thrombolysis: Diagnostic vs. Therapeutic Ultrasound", <u>Ultrasound in Medicine and Biology</u> , Vol. 27, No. ER12, 2001, Pergamon Press, pp.1683-1689.	
/	57	Chen et al, "MRI Study of Immediate Cell Viability in Focused Ultrasound Lesions in the Rabbit Brain", <u>Journal of Magnetic Resonance Imaging</u> , Vol. 13, 2001, pp. 23-30.	

<b>Examiner Signature</b>		<b>Date Considered</b>	
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\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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## Sheet

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of

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**Compleat if Known**

Application Number

10/612,171

**Filing Date**

7/1/2003

**First Named Inventor**

Tosaya, Carol A.

Art Unit

Examiner Name \_\_\_\_\_

Attorney Docket Number

02017A

## U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code <sup>2</sup> (if known)			
	25	US-4,617,931	10/21/1986	Dory	Prior Art
	26	US-4,721,106	01/26/1988	Kurtze et al.	Prior Art
	27	US-5,209,719	05/11/1993	Baruch et al.	Prior Art
	28	US-5,269,291	12/14/1993	Carter	Prior Art
	29	US-5,318,014	06/07/1994	Carter	Prior Art
	30	US-5,431,663	07/11/1995	Carter	Prior Art
	31	US-5,709,676	01/20/1998	Alt	Prior Art
	33	US-4,658,828	04/21/1987	Dory	Prior Art
	34	US-33,590	05/21/1991	Dory	Prior Art
	35	US-5,080,102	01/14/1992	Dory	Prior Art
	36	US-5,150,712	09/29/1992	Dory	Prior Art
	37	US-5,247,935	09/28/1993	Cline et al.	Prior Art
	38	US-5,291,890	03/08/1994	Cline et al.	Prior Art
	39	US-5,323,779	06/28/1994	Hardy et al.	Prior Art
	40	US-5,327,884	07/12/1994	Hardy et al.	Prior Art
	41	US-5,647,760	08/19/1997	Ying et al.	Prior Art
	42	US-5,873,845	02/23/1999	Cline et al.	Prior Art
	43	US-6,074,352	06/13/2000	Hynynen et al.	Prior Art
	44	US-6,088,613	07/11/2000	Unger	Prior Art
	45	US-6,135,971	10/24/2000	Hutchinson et al.	Prior Art

## FOREIGN PATENT DOCUMENTS

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Examiner  
Signature

Date  
Considered

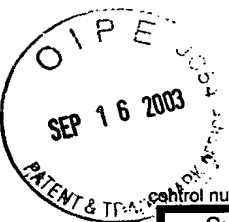
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<sup>2</sup>See Kinds Codes of USPTO Patent Documents at [www.uspto.gov/dm/kinds](http://www.uspto.gov/dm/kinds).  
<sup>3</sup>Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).  
<sup>4</sup>For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.  
<sup>5</sup>Kind of document by the appropriate symbols as indicated on the Applicant's place a check mark here if English language Translation is attached.

document under WIPO Standard ST. 16 if possible. <sup>6</sup>Applicant is to place a check mark here if English language translation is attached.

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				Application Number	10/612,171
				Filing Dat	7/1/2003
				First Named Invent r	Tosaya, Carol A.
				Art Unit	
				Examiner Name	
Sheet	4	of	4	Attorney Docket Number	02017A

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code <sup>2</sup> (if known)			
	49	US-5,752,515	05/19/1998	Jolesz et al.	Prior Art
	50	US-2000/0038086 A1	03/28/2002	Hynynen et al.	Prior Art
	53	US-6,139,819	10/31/2000	Unger et al.	Prior Art
	54	US-6,004,257	12/21/1999	Jacobson	Prior Art
		US-			
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		Country Code <sup>3</sup> - Number <sup>4</sup> - Kind Code <sup>5</sup> (if known)				

Examiner Signature		Date Considered	
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<sup>3</sup>Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup>For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup>Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup>Applicant is to place a check mark here if English language Translation is attached.

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09-22-03.



PTO/SB/21 (01-03)

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<b>TRANSMITTAL FORM</b> (to be used for all correspondence after initial filing)		Application Number	10/612171
		Filing Date	Jul 1, 2003
		First Named Inventor	Carol A. Tosaya & John W Sliwa, Jr.
		Art Unit	
		Examiner Name	
Total Number of Pages in This Submission	1	Attorney Docket Number	02017A

ENCLOSURES (check all that apply)		
<input type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment / Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input checked="" type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Response to Missing Parts/Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____	<input type="checkbox"/> After Allowance Communication to Group <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to Group ( <i>Appeal Notice, Brief, Reply Brief</i> ) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Statement Regarding Prior Art PTO 1449 plus 57 References
Remarks		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT	
Firm or Individual	David W. Collins - Intellectual Property Law
Signature	<i>David W. Collins</i>
Date	September 16, 2003

CERTIFICATE OF TRANSMISSION/MAILING			
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450			
			September 16, 2003
Type or printed	Myra B. Chrsteck		
Signature	<i>Myra B. Chrsteck</i>	Date	September 16, 2003

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time your require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Washington, DC 20231.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Carol Tosaya & John Sliwa, Jr.

Serial No.: 10/612,171

Filed: 7/1/2003

Title: System and Methods for Treatment of  
Alzheimer's and Other Deposition  
Related Disorders of the Brain

Attorney Docket No.: 02017A

Group Art Unit:

Examiner:

Commissioner for Patents  
Washington, D.C. 20231

**INFORMATION DISCLOSURE STATEMENT**

Dear Sir:

This Information Disclosure Statement is submitted:

- ☒ under 37 CFR 1.97(b), or  
(Within three months of filing national application; or date of entry of international application; or before mailing date of first office action on the merits; whichever occurs last)
- ☐ under 37 CFR 1.97(c) together with either a:  
☐ Statement under 37 CFR 1.97(e), or  
☐ a \$180.00 fee under 37 CFR 1.17(p), or  
(After the CFR 1.97(b) time period, but before final action or notice of allowance, whichever occurs first)
- ☐ under 37 CFR 1.97(d) together with a:  
☐ Statement under 37 CFR 1.97(e), and  
☐ a \$180.00 fee set forth in 37 CFR 1.17(p).  
(Filed after final action or notice of allowance, whichever occurs first, but before payment of the issue fee)

☒ Applicant(s) submit herewith Form PTO 1449-Information Disclosure Citation together with copies, of patents, publications or other information of which applicant(s) are aware, which applicant(s) believe(s) may be material to the examination of this application and for which there may be a duty to disclose in accordance with 37 CFR 1.56.

The relevance of the attached references is that this is the closest art of which Applicant is aware.

Applicant submits that the above references taken alone or in combination neither anticipate nor render obvious the present invention. Consideration of the foregoing in relation to this application is respectfully requested.

It is requested that the information disclosed herein be made of record in this application.

Respectfully submitted,

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450



David W. Collins  
Attorney/Agent for Applicant(s)  
Reg. No. 26,857

Date of Deposit: September 16, 2003

Date: September 15, 2003

Typed Name: Myra Best Christeck

Telephone No.: (520) 399-3203

Signature: Myra Best Christeck



PATENT  
D-02017A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

CAROL A. TOSAYA ET AL

Serial No.: 10/612,171

Group Art Unit:

Filed: July 1, 2003

Examiner:

For: SYSTEM AND METHODS FOR TREATMENT OF ALZHEIMER'S  
AND OTHER DEPOSITION-RELATED DISORDERS OF THE BRAIN

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Commissioner for Patents

P. O. Box 1450

Alexandria, VA 22313-1450

STATEMENT REGARDING PRIOR ART

Sir:

This is a Statement Regarding Prior Art in the above-captioned application.

REMARKS

The prior art discussed below includes that discussed in the patent application, as well as art not discussed therein, and is divided into six sections:

- A. prior art targeting of Alzheimer's for therapy and/or diagnosis;
- B. prior art amyloid imaging;
- C. prior-art acoustic lysis or lithotripsy of concretions, clots and plaques;
- D. prior art devices for performing acoustic tissue-therapy in the body; and
- E. prior art devices for performing acoustic therapy in the brain.
- F recently funded relevant ongoing research programs.

Each section is now discussed separately.

A. Prior Art Targeting of Alzheimer's for Therapy and/or Diagnosis.

WO95/19178 application to Iqbal, discussed in the application, describes the administration of therapeutic molecules to the patient which increase the activity of protein phosphatases towards abnormal hyperphosphorylated tau, the major protein subunit of paired helical filaments in neurofibrillary tangles. A variety of administration means are described, including intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral for the therapy molecules, which can cross the blood-brain barrier. Controlled release liposomes are also described. In addition, a means of using the inventive approach to diagnose Alzheimer's is also described.

U.S. Patent 5,478,857 to Clemens et al describes the therapeutic administration of an inhibitor of phospholipase A-Two, especially cytosolic phospholipase A-Two. Additional histological description of deposits in the parenchyma and cerebral vasculature are mentioned. It is also mentioned that senile plaques are invariably surrounded by dystrophic neurites. Evidence that Alzheimer's is associated with an inflammatory response and that non-steroidal anti-inflammatories can slow the pace of the diseases progress are also presented.

U.S. Patent 5,750,349 to Suzuki et al describes the use of antibodies that bind specifically to beta-amyloids or derivatives thereof by recognizing their N-Terminal, C-Terminal or other central molecular features of beta-amyloids. These antibodies are proposed as useful for both diagnosis and therapy applications.

U.S. Patent 5,837,853 to Takashima et al describes a diagnostic and therapeutic means employing an inhibitor of tau-protein kinase 1. He also describes the general shrinkage of the cerebral cortex seen in Alzheimer's patients. The specific mechanism of excess amyloid-beta protein deposited in neurons is described, as is the distribution of molecular weights of the tau proteins.

U.S. Patent 5,886,051 to Bergeron et al describes an active therapeutic agent that is a particular class of polyamine of natural or synthetic design.

U.S. Patent 5,889,042 to Maclean et al describes a molecular structure which is proposed to be effective against diseases which are known to be inhibited by an estrogen, an antiestrogen or estrogen agonist. Alzheimer's is one such disease.

U.S. Patent 5,955,317 to Suzuki et al describes again terminal-recognizing antibodies

U.S. Patent 5,962,463 to Nitsch et al describes stimulating non-amyloidogenic processing by the activation of cell-surface serotonin receptors linked to phospholipase and protein kinase-C.

U.S. Patent 6,028,066 to Unger describes novel prodrugs comprising fluorinated amphiphiles and methods and means to make and deliver them.

U.S. Patent 6,043,224 to Lee et al describes compositions and methods of regulating APP overexpression and mediating reactive astrogliosis through cAMP signaling or the activation of beta-adrenergic receptors.

U.S. Patent 6,080,582 to Alkon et al is primarily aimed at diagnosis. Differences between potassium channels in cells from Alzheimer's patients and normal donors are detected, as are differences in intracellular calcium concentrations between Alzheimer's and normal cells in response to chemicals known to increase intracellular calcium levels.

U.S. Patent 6,190,691 to Mak describes methods of screening therapeutic compounds capable of suppressing cytokine production. The focus is on inflammatory response blockage.

U.S. Patent 6,300,085 to Alkon is similar to US Patent 6,080,582 above, also to Alkon. "Brain to Plasma Amyloid-Beta Efflux: A Measure of Brain Amyloid Burden in a Mouse Model of Alzheimer's Disease" by DeMattos et al, Science Magazine, Vol. 295, p. 2264 (22 March 2002) describes the peripheral administration of a monoclonal antibody to beta-amyloid which allows for an assay of amyloid burden.

Finally we have the out-of-numerical patent-number order but related set of U.S. patents 5,980,480 to Rubenstein et al of CS Fluids Inc., “Method And Apparatus For Treating Adult-Onset Dementia of The Alzheimer’s Type”, 6,264,625 to Rubenstein et al of CS Fluids Inc., “Method And Apparatus For Treating Adult-Onset Dementia Of The Alzheimer’s Type”, and 6,383,159 to Saul et al of Eunoe Inc. (CS Fluid’s corporate successor), “Devices And Methods For Removing Cerebrospinal Fluid From A Patient’s CSF Space”. Uniquely from most of the other prior art discussed herein, these cover the shunt-drainage of small but controlled amounts of cerebrospinal fluid from Alzheimer’s patients brain cavities. Limited data to date seems to show that such drainage combined with the natural bodily replacement of said drained fluid effectively dilutes toxic materials which otherwise build up in the CSF cavities. These toxic species include some of the known plaque proteins or fragments thereof associated with Alzheimer’s. Such limited data show arrested or at least slowed cognitive decline of at least some AD patients. The FDA has approved an ongoing much-larger study involving 26 hospitals and 256 patients. Essentially these patents apply, in a novel way, known hydrocephalus shunt-drainage techniques to AD patients wherein instead of relieving high CSF pressure one is causing volumetric turnover of CSF to reduce the otherwise excessive accumulation of toxic AD by-products (or so it is thought by several researchers). There is no application or suggestion of therapeutic ultrasound as applied to AD patients taught in any of these references.

It will be noted that with the exception of the CSF/Eunoe shunt system these are all stand-alone drug or medicament-related diagnosis or therapy tools.

#### B. Prior Art Amyloid Imaging.

WO 97/26919 to Caprathe et al describes the difficulty of directly imaging amyloid plaques using MRI or CAT. Caprathe also describes prior unsuccessful attempts at antibody-labeling of AD plaques to better image them. The patent application goes on to teach specific labeling compounds which offer superior imaging performance over the prior art.

WO 97/41856 to Lansbury describes novel organometallic compounds for binding to amyloid. The patent application goes on to describe imaging methods using these compounds to visualize amyloid deposits. Imaging can be used to also monitor the progress or stoppage of any AD disease state.

U.S. Patent 6,001,331 also to Caprathe et al further describes the above use of radio-labeled labeling compounds for imaging as well as for therapy.

### C. Prior-Art Acoustic Lysis or Lithotripsy of Concretions, Clots and Plaques.

U.S. Patent 3,492,531 to Hoff et al describes one of the earliest lithotripter devices for smashing kidney stones or gallstones. These devices have large (fraction of a meter) diameter acoustic horns energized by spark discharge or large piezoceramic emitters. In this patent, x-rays are used to locate the stones and in later historical work, ultrasound imaging is also used for image guidance. Unlike AD plaques, stones can be easily seen because they have substantial x-ray and/or ultrasonic imaging contrast in their natural form and they are generally brittle. Most often, stones and concretions not only have imaging contrast but they are surrounded by organ tissues, which are not nearly as susceptible to damage as is brain tissue. Thus, poor aiming of a conventional lithotripter typically results in inconveniently not smashing the stones and having to re-aim the apparatus, as opposed to a miss, causing permanent brain damage in the AD application of inventors' disclosure herein.

U.S. Patent 4,311,147 to Hausler describes a device similar to that above, but incorporates features allowing for multiple shocks. It is also water- or bag-coupled to the target organ. Again, pulverizing shocks are used and are delivered through tissue only.

U.S. Patent 4,486,680 to Bonnet et al describes a "grab and smash" device that is inserted into the body. The calculus is grabbed and pulverized in-situ with closely coupled acoustic shock waves. The device is especially suited for urethra and kidney stones wherein the device can gain access through a natural lumen. Note that herein the ultrasonic transducer is external and passes its acoustic waves into a waveguide running to the basket. Again, we note that this device and all devices so far in this section are able to target isolated or isolatable brittle stones residing in bodily-liquid-filled organ cavities, generally one at a time.

U.S. Patent 4,526,168 to Hassler et al describes yet another externally applied calculi smasher, but with ultrasonic imaging capabilities as well as with improved and more reliable horn design. Again, it is water coupled and again, it uses very high smashing energies at its remote focus.

U.S. Patent 4,617,931 to Dory describes yet another similar device again operating to deliver  $10^8$  pascals of smashing overpressure to the concretion. Its improvements include a spherical piezo emitter and a cointegrated sector ultrasonic- imaging probe. Note that “skullcap” as used therein is merely an affectionate common name for the general shape of the emitter; it is NOT used on the skull but is used, via a liquid standoff, into soft body tissues and underlying organs.

U.S. Patent 4,721,106 to Kurtze describes an improved spherical piezoelectric emitter for smashing stones. Its advantage is better control of the negative-going pulse at the focal site. Such rarefaction pulses cause violent inertial cavitation. Cavitation in any kind of living soft tissue can cause cellular destruction. Kurtze provides a means of preventing cavitation damage to the organs around a stone that may still be close to the emitter focus. For more data on cavitation damage to living tissues consult “Acoustic Cavitation and Capillary Bleeding” by Rott included herein.

U.S. Patent 5,209,719 to Baruch et al describes a lumen-based device for treating lumen-based plaques or stenosis (i.e., intravascular blockages) having an external transducer and a tubular waveguide. Fluids are delivered through the tube for cooling and for flushing of stenosis debris after smashing.

U.S. Patent 5,269,291 to Carter et al describes a similar device to that of US Patent 5,209,719, but instead incorporates the excitation transducer in the head of the catheter with only a small vibrating rod or exciter mounted on the transducer. This reduces acoustic losses. Again, the mechanical smashing and cavitation mechanisms are mentioned as desirable. Note the macroscopic tip displacements of 6 or so microns at 100KHz driving frequency. These are again indicative of the high power needed for mechanical smashing.

U.S. Patent 5,318,014 again to Carter et al describes another device similar to his device of the above patent. The significant points here, relative to the present inventors’ own application herein, are that an agent liquid is used to both increase cavitation and thereby enhance erosive clot removal. He also describes using streptokinase to further enhance clot dissolution. It is blood-clot specific and unusable for brain plaques. In all embodiments, the erosive power of the cavitation bubbles dominates, even with the drug.

U.S. Patent 5,431,663 also to Carter describes some further improvements in acoustic transducer and acoustic amplifier designs for the above-type of intraluminal devices.

U.S. Patent 5,709,676 to Alt describes the use of both a laser-induced mechanical shock-wave and a drug operating through fissures in the plaques cause by the shock waves. The laser shockwave is first applied, then the drug, in two minute intervals. The clot-dissolving drug is described as a urokinase, streptokinase or rTPA. The required optical fiber runs the length of the catheter. Essentially, a sequence of laser-induced clot shocks and intervening drug treatments are performed.

Finally, we have "Lysis and Sonoporation of Epidermoid and Phagocytic Monolayer Cells by Diagnostic Ultrasound Activation of Contrast Agent Gas Bodies" by Miller et al, Ultrasound in Medicine & Biology, Vol. 27, No 8, pp. 1107-1113, August 2001. The main point of including this paper is that it demonstrates that even low-power diagnostic-imaging ultrasound is capable of sonoporation (causing leakage into a cell) and lysis (cell membrane damage) when gas-bubble based ultrasound contrast agents are used. Thus, microbubbles cavitating in the presence of healthy brain cells can be expected to damage healthy brain cells. Hynynen (discussed below) cavitates them at the brain lumen BBB and not among the brain cells residing around the lumens.

#### D. Prior Art Devices for Performing Acoustic Tissue-Therapy in the Body.

U.S. Patent 4,658,828 to Dory teaches an acoustic therapy device for multicycle delivery of heating acoustics to a focal point such as a tumor to be killed. Acoustic imaging is cointegrated. What is important here, and for the following patents, is that rather than single-pulse smashing of large stones, we are seeing many-pulse lower-intensity heating of targets to thermally damage them. So the mechanism is thermal and not mechanical. Soft tissues are being treated as opposed to stones or hard bloodclots.

Re. 33,590 is a reissue of the above patent.

U.S. Patent 5,080,102 also to Dory describes further refinements involving interspersing of treatment and imaging steps, both using acoustic transducers.

U.S. Patent 5,150,712 also to Dory describes further improvements of the above hardware.

U.S. Patent 5,247,935 to Cline et al describes the use of a hyperthermia (heating) transducer for surgery also using an MRI imaging machine which is capable of seeing (imaging) the heated tissues directly. In other words, the heating can be aimed and can be measured. The focus of the patent is on the MRI integration advantages.

U.S. Patent 5,291,890 also to Cline et al describes additional pulsed heat sources for use with MRI guided hyperthermia.

U.S. Patent 5,323,779 to Hardy et al describes more detail for the operation and pulse-timing of the above two MRI-guided hyperthermia surgery devices.

U.S. Patent 5,327,884 also to Hardy et al further describes system details applicable to MRI-guided hyperthermia surgery.

U.S. Patent 5,657,760 to Ying et al describes ways of utilizing Doppler ultrasound methods to measure therapy temperatures and to monitor the extent of tissue treatment. As a general comment, the MRI methods are regarded as the best means of currently accomplishing these goals, particularly if in-situ dynamic temperatures are to be tracked.

U.S. Patent 5,873,845 to Cline et al describes a means of spreading out the focus of a hyperthermia transducer in order to reduce the amount of physical scanning of the target which is required to hit the entire diseased portion. Unfortunately, the energy density is also spread out and the peak achievable heating rate suffers for his taught application.

U.S. Patent 6,074,352 to Hynynen et al describes the use of hyperthermia using ultrasound for the treatment of joint diseases. While the pannus can be obliterated in a lab dish, it is extremely difficult to do this through bone as is required in living humans. So it is of academic interest mainly and has not progressed to product development.

U.S. Patent 6,088,613 to Unger describes delivering a vesicle-based contrast medium viewable in MRI, using MRI to decide where the disease resides, and then using focused ultrasound to release drug agents from vesicles selectively residing in the disease area.

U.S. Patent 6,135,971 to Hutchinson et al describes the use of an aperiodic ultrasound array to reduce unwanted sidelobes during ultrasound hyperthermia. Unfortunately, not mentioned, is that such a scheme degrades imaging performance. This is why most current attempts to both ultrasonically image and deliver therapy utilize separate therapy and imaging transducers.

WO 94/23308 application to Hardy et al covers similar ground to the above MRI-guided hyperthermia patents.

E. Prior Art Devices for Performing Acoustic Therapy in the Brain.

A. Malcolm in “Ablation of Tissues using High-Intensity Focused Ultrasound”, discussed in the application, describes the history of focused ultrasound surgery R&D for the brain going back to 1942. (see attached paper).

WO 98/07373 to Hynynen describes a therapy device for delivering ultrasound into the skull. Hynynen was one of the first to demonstrate that focused ultrasound could be delivered through the intact skull with an intensity and focus sufficient at least to ablate macroscopic rabbit-brain targets. However, this reference teaches primarily direct cavitation induced damage “therapy”. We have explained that even for soft-tissue acoustic-necrosis (wherein acoustic introduction is usually through highly favorable “transparent” skin or organ-surface tissues), cavitation is avoided as it cannot be controlled, its distribution has a degree of randomness to it, and adjacent and/or intervening healthy cell membranes are burst. Thus, we know of no practical cavitation-centric therapy device for random use in the brain operating from the skull surface. Secondly, this reference runs the risk of causing cavitation at the blood-brain barrier or adjacent the skull interior surface with unknown consequences. It will be noted that Hynynen’s own Fan reference of ‘07373 almost immediately states that cavitation is to be avoided. This reference (‘07373) mentions but does not explain necrosis (heating) approaches. It does at least mention that perfusing blood in the brain makes it quite difficult to create and/or maintain a finely focused hot spot. What Hynynen has shown is that one may focus an ultrasound beam to a few mm diameter within the brain if enough corrections are made to phase errors caused by the nonuniform skull. His preferred embodiments involve high skull-coverage (to get significant power or focal gain) and detailed phase corrections for varying bone structure. High acoustic power and gain at his focus is achieved by beam steering electronically. The approach probably also requires MRI imaging of the hot spot in a setup mode, as he has more recently published upon. Thus, in the view of the present inventors, for a patient with a macroscopic tumor, for example, wherein a high-coverage focused acoustic skullcap can be used with full phase corrections to account for skull variations from point-to-point, this may be a useful therapy for isolated tumors

wherein a beam-formed beam is codirected at the tumor from multiple transducers.. This also assumes the availability of MRI temperature imaging equipment. In fact, the recent research trend is the use of open-arm MRI systems in which a patient can be placed and operated upon in-situ. In this manner ultrasound ablation (necrosis) can be aimed in real time. This is all well and good, but it is very very expensive to combine the ultrasound therapy and MRI equipment, very, very time consuming, and does not at all address distributed Alzheimer plaques found in MILLIONS of patients. These cannot be corrected via direct cavitation or burning without unacceptable side-effects. They also cannot be cost-effectively corrected with a tool(s)/facility that costs millions of dollars and are thereby few (compared to the millions of patients) in number.

U.S. Patent 5,752,515 also to Jolesz and Hynynen is directed to the focused acoustic delivery of drugs through the blood-brain barrier (BBB) under MRI imaging guidance. Its operating assumption is that the needed drug is relatively impermeable to the BBB by itself. Note first that acoustic drug delivery itself through this barrier was previously demonstrated in prior art that they reference. The '515 reference teaches targeting (using cavitation, heating or amassed contrast agent verification thereof) and subsequent drug delivery through the BBB to the verified site. It will be noted that the preferred imaging tool is MRI (or perhaps PET). Thus, we again have a very very expensive low-throughput arrangement. Again, the therapy (delivery of a self-acting drug) is targeted at a small point or volume of a few cubic millimeters or a  $\text{cm}^3$  at most per the teaching. No drugs to treat Alzheimer's or to remove Alzheimer's plaques are suggested or taught. No use of the ultrasound itself to treat Alzheimer's or related plaques is described. No combined or synergistic drug/ultrasound therapy is taught. As a matter of completeness, the present inventors also wish to point out that while urging the drug across the BBB has been historically proven as possible, what has not been proven is that the drug can be uniformly delivered to all the brain material encompassed by the beam. The BBB walls are not uniformly distributed and have a wide variety of angles to the beam, including zero degrees. Thus, some spots of BBB-opening failure can also be expected.

Moving now to U.S.2002/0038086 A1, also to Hynynen, this seems to be an elaboration on U.S. Patent 5,752,515 above. He has extended the scope of discussion to blood-organ barriers wherein one such organ is the brain. He teaches the use of bubble-type contrast agents to induce cavitation in the brain vasculature, thereby opening the BBB surrounding that vasculature and

admitting an imagable contrast agent to verify such opening of the local BBB. The bubbles greatly reduce the acoustic energy required to cause cavitation from the above references. Again, note that he is opening the BBB surrounding the brain vasculature so that another unspecified drug may leak into the adjacent brain cells through the damaged BBB and perform a therapeutic purpose on its own. The drug makes it into the brain but the bubbles burst in the vasculature and are too big to leak across even an undamaged BBB. It is to be noted that neither Alzheimer's nor plaque is mentioned and that it is the opening of the BBB which is the focus, not the selection of the drug to be delivered through the BBB nor what that drug is to do or whether it can be acoustically activated. Certainly, the action of such a BBB-penetrating drug in the brain, particularly with regard to the effect of any acoustics on it, is not discussed or taught as desirable. It is the "first-step", getting something through the BBB, that is the focus here.

Chronologically moving ahead, we now have the reference "Micro-Receiver Guided Transcranial Beam Steering", Clement, G. and Hynynen, K., IEEE Transactions On Ultrasonics, Ferroelectrics and Frequency Control, 2002, vol 49, no 4, pp 447-453, IEEE Institute Of Electrical And Electronics. Therein is demonstrated the use of an acoustic hydrophone situated in the target region used to correct firing phases of the multiple external transducers to overcome arrival-time aberrations. It is done in the skull as opposed to the micro-receiver prior art, which was demonstrated in soft tissues. It makes an otherwise non-invasive process into a minimally invasive process. It has no direct bearing on our invention herein nor makes any reference to Alzheimer's plaques. It does verify certainty of focus if one needs a fine focus. It essentially teaches its use as a focus tune-up aid for in-skull application.

Moving next to "Transcranial Ultrasound-Improved Thrombolysis: Diagnostic vs. Therapeutic Ultrasound", Behrens, S et al, Ultrasound In Medicine And Biology, 2001, vol 27, No. ER12, pp 1683-1689, Pergamon Press, we see that those inventors show additional data (over their references) demonstrating that low-frequency low-power ultrasound is able to accelerate the breakup of blood clots in the presence of rt-PA and that sufficient ultrasound to do this should be deliverable through the skull at least through the temple regions. Their references also mention some undesirable side-effects seen in human brain tissues due to low intensity ultrasound-effects relating to inflammation and intracellular calcium levels. Note the avoidance of cavitation as well as the avoidance of opening the blood-brain barrier in his rat subjects. Rt-PA is a widely and

long known blood clot dissolver and is highly specific to blood clots via an enzymatic reaction. They do not mention brain diseases, Alzheimer's or plaques nor do they discuss any medications or therapies useful therefore.

U.S. Patent 6,139,819 to Unger et al is an informative tome on the subject of designing contrast agents. In particular, his focus therein is on acoustic contrast agents used to image and treat blood clots associated with arrhythmia. Such contrast agents are designed to recognize and attach to the blood clot thrombi or coagula using biomedical or molecular biology principles. In general, a targeting ligand coats the contrast agent and that ligand selectively targets a receptor on the blood clot fibrin material. Once the targeted contrast agent has "decorated" the target clot, it can then not only provide improved image contrast but it can also be broken using the ultrasound beam to release a therapeutic drug-payload contained inside of the contrast agent particles or vesicles. Unger et al describe such drug release from contrast agents for blood-clot therapy. They also mention that the microbubble breaking event can provide further mechanical disruption to the blood clot.

U.S. Patent 6,004,257 to Jacobson relates to the proposed use of magnetic and electromagnetic therapy to ameliorate the aging processes. It is an interesting concept requiring some hard evidence of workability, which is currently lacking. It has no bearing on the present invention.

WO 02/09608 A2 to Hynynen et al is the same material as US2002/0038086 A1 covering the opening of the blood brain barrier (BBB). All of the above commentary applies.

EP1175920A1 to Alexandrov et al describes the use of trans-skull ultrasound to overcome the damage caused by ischemic strokes. In particular, that damage is caused by blood-clots in the brains vasculature which starve large regions of the brain of blood and thereby cause brain cell death over an area larger than the clot. The benefits for stroke treatment are described as accelerated clot dissolution and, in addition, improved delivery of medicaments to ischemic tissue and beneficially improved perfusion. However, the employment of multiple "probes" at angles to each other for brain therapy has been described in numerous prior-art including, for example, U.S. Patent 5,752,515 and WO98/07373 above. The use of ultrasound to accelerate clot dissolution is also described in prior art above. Despite the lack of prior-art referencing, it is an interesting piece of work.

The last acoustic brain therapy reference we shall discuss is the paper by Chen et al, "MRI Study of Immediate Cell Viability in Focused Ultrasound Lesions in the Rabbit Brain", Journal of Magnetic Resonance Imaging, Vol. 13, pp. 23-30 (2001). Although this study was done to demonstrate that MRI-imaged ultrasonic-ablated lesion size correlates with histologically measured lesion sizes, it demonstrates the interest in the community for ablation-type (high energy) brain surgery using ultrasound. It has no direct bearing on the invention herein.

The most recent ongoing research projects in the general areas of drugs, diet, social impact and disease-imaging which are approved and funded by the centrally-coordinating Alzheimer's Association itself are now listed below. These can be regarded as designed using the latest understanding of all medical and social aspects of the disease.

#### F. Recently Funded Relevant Ongoing Research.

- (1) Caloric Restriction and Inflammatory Mechanisms in Alzheimer's Disease;
- (2) Effects of Estrogen on Glial Activation and Cytokine Expression in Models of Alzheimer's Disease;
- (3) Cholinergic Hypoactivity Induced by Par-4: Implications for the Treatment of Alzheimer's Disease;
- (4) Genetic Polymorphisms, Endogenous Estrogen Exposures, and Memory Decline;
- (5) The Involvement of Neprilysin and Insulysin in Amyloid-Beta Peptide Catabolism;
- (6) Benzothiazole PET Imaging Probes for Amyloid in Alzheimer's disease;
- (7) Novel Therapeutics for Alzheimer's disease Amyloidosis;
- (8) Longitudinal mRNA Expression Profiling of White Cells in a Cohort of Normal Elderly at Risk for AD: Clinical-Molecular Correlation in the ADAPT Study;
- (9) Lipoprotein Interactions with Amyloid-Beta: Role of ApoAI/HDL in Alzheimer's Disease;
- (10) Discovering the Genetic Basis for Why Centenarians Markedly Delay or Escape Alzheimer's Disease;

- (11) Cognitive Function in Presymptomatic Autosomal Dominant Alzheimer's Disease;
- (12) Regulation of BACE in DIGs;
- (13) Evaluation of Presenilins as Anti-amyloidogenic Targets in Alzheimer's Disease Through the Characterization of PS1/PS2 Conditional Knockout Mice;
- (14) A Protective Role for Diazepam against Neurodegeneration Underlying Alzheimer's Disease;
- (15) Antisense-Based Therapeutics for Alzheimer's Disease;
- (16) Early Detection of AD-like Pathology in Transgenic Mice with MRI and Behavior;
- (17) Functional Anatomic Characterization of DAT with fMRI;
- (18) Manipulation of Endogenous Neural Precursors to Reconstruct Cortical Circuitry;
- (19) Mechanism of the Action of Donepezil on the Beta-Amyloid Proteins;
- (20) Mechanisms of Muscarinic Acetylcholine (mAChR) Dysfunction in Alzheimer's Disease;
- (21) Perceptual Mechanisms of Visuospatial Disorientation in Alzheimer's Disease;
- (22) Potential Impact of NBAC's Recommendations on Dementia Research;
- (23) Strategies for Prevention of Amyloid Beta (Ab) Toxicity in the Primate Brain;
- (24) The Role of Antibodies to Amyloid Beta (Ab) Protein in Preventing and Treating Alzheimer's Disease;
- (25) Estrogen Therapy and the Effects of Cognition-Enhancing Agents in Aged Rhesus Monkeys;
- (26) Plasmin as a Modulator of Ab Levels and Actions;
- (27) Nutritional Modulation of Accelerated Alzheimer-Type Phenotype in Transgenic Mice Carrying both Mutant Amyloid Precursor Protein and Presenilin 1 Transgenes;
- (28) In Vivo Measurement of A-Beta Amyloid Deposition;

- (29) Effect of Estrogen on the Cholinergic System;
- (30) Regulated Transgenic Models to Test Novel Treatment Strategies for Alzheimer's Disease;
- (31) Tau Protein Cross-Linking in Alzheimer's Disease;
- (32) Estrogen Modulation Effects on Cholinergic Function in Normal Post-Menopausal Women and Individuals with Alzheimer's Disease;
- (33) Cyclooxygenase and Complement Gene Expression in Neurodegeneration and Alzheimer's Disease;
- (34) Neuroprotective Actions of Sex Steroid Hormones and Their Therapeutic Relevance to Alzheimer's Disease;
- (35) Progression of Cerebral Amyloid Angiopathy in a Mouse Model;
- (36) Dietary Modulation of the Risk of Alzheimer's Disease: Effects of Dietary Cholesterol and Vitamin E on the Alzheimer's Disease Phenotype of a Transgenic Mouse Model;
- (37) Steroid Synthesis and Its Role in the Preservation of the Songbird Hippocampus;
- (38) FDDNP-PET Imaging for Early Detection of Alzheimer's Disease;
- (39) A Double-Blind Study of Donepezil With and Without Thyroid Hormone in the Treatment of Alzheimer's Disease;
- (40) Functional Magnetic Resonance Imaging (fMRI) of Cognitive Changes in Normal Elderly Subjects and Patients with Probable Alzheimer's Disease (pAD);
- (41) Validation of a Diagnostic Marker for Early Intervention in Alzheimer's Disease;
- (42) Role of Estrogen and Presenilin 1 in Beta-APP Trafficking and Amyloid Beta Formation: Implication for Disease Intervention;
- (43) Crystal Structure Determination of Soluble Amyloid Beta in Complex with Proteins;
- (44) Magnetic Resonance Microscopy and Alzheimer's Disease: Early Detection of Alzheimer's Pathology in Transgenic Mice Overexpressing Beta Amyloid Protein;

(45) Functional Magnetic Resonance Imaging (fMRI) of Nondemented Older Adults at Risk for Alzheimer's Disease;

(46) Comprehensive Preclinical Behavioral Profile of Individuals at Genetically Defined Risk (Apolipoprotein E) for Alzheimer's Disease;

(47) Detection and Correction of Cognitive Deficits via Visual Manipulation in Alzheimer's Disease;

(48) Anticipatory Dementia: A Path to Early Detection of Alzheimer's Disease;

(49) PET Cognitive Activation in Mild Cognitive Impairment;

(50) Pathways to Alzheimer's disease: Identifying Factors That Promote or Inhibit Early Detection;

(51) Screening Strategies to Identify Drugs That Suppress the Immunopathology of Alzheimer's Disease;

(52) Oxidized Protein Biomarkers for Early Detection of Alzheimer's Disease;

(53) Vascular-Mediated Neuronal Death in Alzheimer's;

(54) A Pilot Study to Identify Individuals at High Risk of Alzheimer's Disease in a Community Population of Older African Americans;

(55) Validation of a Novel Diagnostic Test for Alzheimer's Disease;

(56) Noradrenergic-Cholinergic Interactions: Implications for Alzheimer's Disease;

(57) A Transgenic Mouse Model of Familial Creutzfeldt-Jakob Disease;

(58) Risk Factors and Initial Signs of Primary Progressive Dementia in Subjects at Increased Risk for Alzheimer's Disease;

(59) An Age-of-Onset Determinant for Alzheimer's: Identification of a Novel Target;

(60) Discovery of Fyn SH2 Domain Ligands As Potential Alzheimer Therapeutics;

(61) Forgetfulness: What's Normal and What's Not;

(62) The Relationship of Culture, Education, and Literacy to Aging and Dementia among a Random Sample of Community-Dwelling African Americans;

- (63) Early Events in Fibrillogenesis of  $\beta$ -amyloid Examined by NMR Spectroscopy of Fibrils and Soluble Derivatized Congeners;
- (64) Microtubule-Stabilizing Drugs and Alzheimer's Disease;
- (65) Quantification of Oxidative Damage to the Brain in Patients with Alzheimer's Disease;
- (66) Development of a Measure for Early Detection of Cognitive Loss in Alzheimer's Disease: A Psychophysics Approach;
- (67) Improving Diagnosis: Longitudinal Neuropsychological Assessments and Biological Markers in Patients with "Typical" Alzheimer's Disease and the Lewy Body Variant;
- (68) Prevalence of Alzheimer's Disease in a Population-Based Study of Centenarians: What Is Normal Aging versus Disease?;
- (69) Prophylactic In Vivo Gene Delivery to Prevent Death of Entorhinal Neurons;
- (70) PET, APOE, Aging, and the Preclinical Course of Alzheimer's Disease;
- (71) Regulation of Muscarinic Acetylcholine Receptor Responses by RGS (Regulators of G Protein Signaling) Proteins;
- (72) Communication Strategies As Early Indicators of Alzheimer's Disease;
- (73) Assessment of Mild Cognitive Impairments in Nondemented Elderly Assessed by Magnetic Resonance Spectroscopy and Imaging;
- (74) New Triterpenoids As Agents for Prevention and Treatment of Alzheimer's Disease;
- (75) The Role of Caspase-Mediated Cleavage of Presenilins in Alzheimer's Disease;
- (76) Divalproex Sodium Therapy for Agitation in Nursing Home Patients with Dementia;
- (77) Mechanisms Underlying Estrogen/Neurotrophin Interactions in the Brain;
- (78) Metabotropic Glutamate Receptors and Early Cognitive Deficits in Alzheimer's Disease;
- (79) Alpha-Synuclein, NAC, and the Diagnosis of Alzheimer's Disease;
- (80) Seeking a Diagnosis of Alzheimer's: Supports and Barriers;

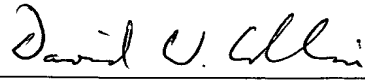
- (81) Characterization of Diffusible Mediators of Tau Protein Polymerization in Cerebrospinal Fluid;
- (82) Detection of Alzheimer's Disease Pathology In Vivo;
- (83) Intracellular Amyloid Accumulation and Its Role in Neuronal Apoptosis;
- (84) Etiologic and Therapeutic Role for Cholinergic Mechanisms in Alzheimer's Disease;
- (85) Aggregated Beta-Amyloid: Assessment and Treatment of Behavioral and CNS Toxicity;
- (86) Correlation of Cholinergic Reserve and Cognitive Function with Positron Emission Tomography;
- (87) Development of Treatments to Control the Immunopathology of Alzheimer's Disease;
- (88) Estrogen Effects on Associative Learning in Alzheimer's Disease: Human Studies and an Animal Model;
- (89) fMRI Measures of Short-Term Memory in Incipient Dementia;
- (90) Non-invasive Diagnosis of Alzheimer's Disease Using Optical Spectroscopy;
- (91) The Search for Combinations of Neuromodulators That Enhance Synaptic Plasticity;
- (92) Peptide Mimetics of Nerve Growth Factor Prevent Neuronal Death;
- (93) Managing the Treatment of Alzheimer's Disease with Metabolic Imaging;
- (94) Neocortical Projection Precursors: Purification, Characterization, Cell Line Generation, and Transplantation to Reconstruct Circuitry After Targeted Apoptotic Neurodegeneration;
- (95) Novel Mechanisms for Establishment and Maintenance of Neuronal Connections;
- (96) An MRI Study of Functional and Anatomical Changes in Aging and Alzheimer's Disease; and
- (97) Reversal of Immunotoxic Lesions of the Basal Forebrain.

The foregoing references are cited and discussed, in conjunction with Applicants' specification, as part of Applicants' duty to disclose all prior art of which they are aware, under 37

CFR 1.56. If the Examiner has any questions, he is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,

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